# EXHIBIT 19

# Pre-existing Hypertension and the Impact of Stroke on Cognitive Function

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**Hypertension has been associated with subclinical injury in the brain and may therefore increase the impact of an incident stroke on cognitive function. The Study of Osteoporotic Fractures (SOF) is a prospective, observational study of 9,704 women aged 65 years and older recruited from four U.S. metropolitan areas. Blood pressure was measured at study entry, and cognitive decline was defined by the change from prestroke to poststroke cognitive testing. During an average follow-up of 6.8 years, incident stroke occurred in 260 participants (3.1%) who had previously completed baseline cognitive testing. Among participants with stroke, 119 completed follow-up cognitive testing a median of 1.9 years after the stroke, 80 died before the next study visit, and 61 did not complete further cognitive testing. After adjustment for demographic factors and other confounders, pre-existing hypertension was a strong predictor of cognitive decline when a stroke occurred (odds ratio [OR], 4.07; 95% confidence interval [CI], 1.37–12.1). In contrast, hypertension was only weakly associated with cognitive decline in the absence of stroke (OR, 1.13; 95% CI, 1.04–1.22) ($p$ for interaction = 0.032). Pre-existing hypertension in women is associated with a greater impact of stroke on cognitive function, possibly by influencing the ability to tolerate or recover from brain injury.**

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Dementia is present in about a fourth of patients after stroke.[1,2] The development of dementia after stroke appears to be related to characteristics of both the stroke and the individual in whom the stroke occurs. For example, although stroke size and location are predictors of dementia after stroke, so are patient-level factors such as age and education level.[3,4] The identification of these patient-level factors is important because they suggest that certain traits or health conditions present before stroke could influence a person's susceptibility to cognitive decline when a stroke occurs. Such differences in susceptibility may provide insight into factors that either augment or detract from a person's ability to adapt to or recover from brain injury.

Vascular risk factors, especially hypertension, are known to be associated with several forms of structural injury in the brain, including silent or covert infarcts and leukoaraiosis.[5–7] In previous cross-sectional studies, the presence of this subclinical injury has been correlated with lower cognitive function after stroke, suggesting that it may increase susceptibility to cognitive impairment when a stroke occurs.[8,9] The interpretation of these studies is limited, however, by their inability to measure the change in cognitive function associated with the stroke event. Their findings could be explained, for example, if pathology such as silent infarct had resulted in lower cognitive function before stroke occurrence. We hypothesized that stroke would have a greater impact on cognitive function, as defined by the change from prestroke to poststroke cognitive testing, in individuals with hypertension when compared with individuals who were normotensive before stroke. We tested this hypothesis in a large, prospective cohort study that made detailed measurements of both stroke incidence and longitudinal changes in cognitive function.

## Subjects and Methods

The study population consisted of 9,704 primarily white, community-dwelling women who were participating in the Study of Osteoporotic Fractures (SOF). Details of the SOF cohort and study procedures have been published previously.[10] Briefly, SOF is a prospective study of risk factors for fractures and physical and cognitive decline among community-dwelling older women. Subjects were recruited regardless of osteoporosis status between 1986 and 1988 from population-based lists in Baltimore, Maryland; Minneapolis, Minnesota; Portland, Oregon; and the Monongahela Valley in Pennsylvania. Subjects were between 65 and 99 years old, were able to walk without the assistance of another person, and were not institutionalized. Interviews, question-

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naires, and examinations were performed at study enrollment and at follow-up visits performed approximately every 2 years.

### *Risk Factor Measurements*

Blood pressure was measured with a mercury sphygmomanometer at the baseline visit (Visit 1) with subjects in a supine position after at least a 5-minute rest. Information about current and past diuretic use was also gathered at Visit 1 by interview and examination of current medicines, with pictures of commonly prescribed tablets available for review. Participants were asked to bring their medications to subsequent visits, and at Visit 4, current use of other types of antihypertensive medications was recorded. Hypertension was defined as a systolic blood pressure greater than 140mmHg, a diastolic blood pressure greater than 90mmHg, or taking an antihypertensive medication at Visit 1 or 4. Tobacco use was assessed by interview. Diabetes was defined by self-report of physician-diagnosed diabetes, insulin use, or both.

### *Stroke Ascertainment and Validation*

Potential strokes were ascertained using a biannual questionnaire in which participants indicated whether a physician had told them that they had a stroke during the past year. Death certificates and hospital records, when applicable, were obtained for all study participants who died before completion of the questionnaire. For all potential strokes, hospital records, results of radiology tests, and outpatient physician records were obtained when possible. Stroke was defined as a rapidly developed clinical sign of focal or global disturbance of cerebral function lasting more than 24 hours or until death with no apparent nonvascular cause.[11] Strokes were classified as atherothrombotic when an individual had an ischemic stroke and there was no information to suggest a cardiac or transcardiac source, global hypoperfusion, or stroke caused by systemic disease or other uncommon cause. Strokes classified as cardioembolic were those that occurred in association with a major cardiac source including atrial fibrillation, mechanical prosthetic heart valve, endocarditis, or cardiac thrombus. All cases of stroke were adjudicated by the site investigators and by both a neurologist and an internist at the SOF coordinating center. Cases for whom there was disagreement were discussed and were considered validated if unanimous consensus was reached. Only validated strokes were considered in this analysis.

### *Assessment of Cognitive Function*

Cognitive function was measured in SOF using three tests: a modified version of the Mini-Mental State Examination (mMMSE),[12] the Digit Symbol Substitution Test (DSST),[13] and the Trails B test.[14] The mMMSE is similar to the standard MMSE but with few questions regarding orientation. The Trails B test is a timed test that requires individuals to connect an alternating sequence of letters and numbers. The score is based on the time needed to complete the sequence, with lower scores reflecting greater degrees of executive function, attention, and visual scanning abilities. The DSST also is a timed, written test that requires individuals to translate numbers into symbols using a key; higher scores indicate increased psychomotor speed, attention, and perceptual organization. The mMMSE was given at study Visits 1, 4, 5, and 6; the DSST was given at Visits 2 and 4; and the Trails B was given at Visits 2, 4, and 6.

Cognitive change was defined as the difference in cognitive test scores between sequential study visits. In participants with stroke, this definition measured cognitive change between the study visit most closely preceding and the visit most closely following stroke to best approximate the impact of stroke on an individual's cognitive test performance. Because previous studies have documented that stroke tends to have a greater impact on measures of cognitive processing speed and executive function when compared with memory and language,[15,16] we used the Trails B test as the primary measure of cognitive function for cohort definition and analysis. In addition, the Trails B was administered on more study visits than the DSST, and therefore allowed analysis of cognitive change after stroke in a larger sample of participants.

### *Statistical Methods*

All between-group comparisons were made using the $\chi^2$ test for categorical variables and the Kruskal–Wallis test for continuous variables. Potential predictors of cognitive change after stroke were analyzed using both multivariable linear and logistic regression. All multivariable models included the following covariates: age, education, baseline cognitive test score, time from stroke to follow-up cognitive testing, and time between baseline and follow-up cognitive testing. The distribution of each variable was examined visually. Because Trails B and mMMSE scores were not normally distributed, we used a logarithmic transformation of scores when using them in linear regression models. In the logistic regression models, cognitive decline was defined dichotomously based on whether the cognitive change between visits was greater than the median change between study visits for the study cohort. We used this definition to maximize power to detect an interaction between pre-existing hypertension and stroke for the risk for cognitive decline. Associations between baseline blood pressure and cognitive decline were analyzed by quartile based on the blood pressures of participants with stroke. We considered the possibility of both linear and J-shaped relations between blood pressure and cognitive decline based on the results of previous studies.[17–19] Linear trend by quartile was assessed using a likelihood ratio test. We used generalized estimating equations to analyze predictors of cognitive decline in analyses of individuals without stroke to adjust for repeated measures of cognitive change in the same individual (eg, one change between Visits 2 and 4 and one change between Visits 4 and 6). All reported $p$ values are two sided. All analyses were performed using the STATA statistical package (Version 8.0; Stata Corporation, College Station, TX).

## Results

During an average follow-up of 6.8 years, incident stroke occurred in 260 (3.1%) of subjects who completed a baseline (Visit 2) Trails B examination. Among these participants with stroke, 119 (46%) completed follow-up Trails B testing at a median of 1.9

*Table 1. Baseline Characteristics of Participants with Stroke by Follow-up Status*[a]

| Characteristic | Follow-up Cognitive Testing Status | | | $p$[b] |
|---|---|---|---|---|
| | Completed (N = 119) | Died (N = 80) | Missing (N = 61) | |
| Age (yr) | 75 ± 4.8 | 79 ± 6.5 | 77 ± 5.2 | <0.01 |
| Education (yr) | 13.0 ± 2.6 | 12.1 ± 2.6 | 11.5 ± 2.5 | <0.01 |
| Hypertension[c], (%) | 83 | 81 | 85 | 0.82 |
| SBP (mm Hg) | 148 ± 21 | 154 ± 21 | 151 ± 19 | 0.09 |
| DBP (mm Hg) | 78 ± 11 | 80 ± 12 | 78 ± 9 | 0.49 |
| Diabetes[d], (%) | 11 | 16 | 26 | 0.04 |
| Current tobacco use (%) | 7 | 14 | 10 | 0.27 |
| History of stroke (%) | 0.8 | 1.3 | 0.0 | 0.70 |
| Baseline Trails B Score[e] | 124 (100–156) | 166 (121–236) | 170 (111–257) | <0.01 |
| Baseline DSST score | 46 (37–53) | 38 (30–44) | 35 (28–44) | <0.01 |
| Baseline mMMSE score | 25 (24–26) | 25 (24–26) | 25 (23–26) | 0.65 |
| Stroke subtype: | | | | |
| Atherothrombotic (%) | 83 | 29 | 79 | <0.01 |
| Cardioembolic (%) | 13 | 41 | 16 | <0.01 |
| Hemorrhagic (%) | 3 | 30 | 5 | <0.01 |

[a]Values presented with a plus/minus sign are means ± SD. Values presented with parentheses are medians (interquartile range).
[b]$p$ values were calculated using the Kruskal-Wallis test for continuous variables and the $\chi^2$ test for categorical variables.
[c]Hypertension defined as SBP >140mm Hg, DBP >90mm Hg, or taking an antihypertensive medication.
[d]Diabetes defined by self-report of physician diagnosed diabetes and/or insulin use.
[e]Note: Higher Trails B scores signify lower performance.

SBP = systolic blood pressure; DBP = diastolic blood pressure; DSST = Digital Symbol Substitution Test; mMMSE = modified Mini-Mental State Examination.

years after the stroke, 80 (31%) died before the next Trails B test was administered, and 61 (23%) did not complete follow-up Trails B testing by the end of the follow-up period (Visit 6). Similar patterns were observed in the percentage of participants with stroke who completed follow-up cognitive testing after first completing either the mMMSE (45%, n = 176) or the DSST (56%, n = 76). Participants who completed follow-up Trails B testing were younger, more highly educated, and less likely to have diabetes at the baseline examination when compared with those who did not complete follow-up testing after a stroke (Table 1). The median time interval between baseline and follow-up Trails B administration was similar when a stroke occurred compared with when there was no stroke between visits (3.90 vs 3.75 years). In participants with stroke who returned for follow-up Trails B testing (n = 119), the median increase in time to complete the Trails B between the prestroke baseline and the poststroke follow-up was 34 seconds (interquartile range, 10–81 seconds). This was compared with a median increase in time to complete the Trails B between study visits of 16 seconds among individuals without an intervening stroke (interquartile range, −7 to 48 seconds) ($p < 0.001$).

### *Impact of Stroke on Cognitive Change in Subjects with and without Pre-existing Hypertension*

In unadjusted analyses, individuals with pre-existing hypertension experienced greater declines in Trails B performance after stroke when compared with those who were normotensive before stroke (median increase in time to complete: 43.5 vs 12.5 seconds; $p = 0.005$). In contrast, there was no association between the presence of diabetes ($p = 0.42$) or tobacco use ($p = 0.57$) ascertained before stroke with the change in Trails B score after stroke. In multivariable linear regression models, the association between pre-existing hypertension and change in Trails B score after stroke was not attenuated by adjustment for age, education, baseline score, time between baseline and follow-up cognitive testing, time from stroke to follow-up cognitive testing, and stroke subtype (adjusted $p = 0.001$). A similar association between pre-existing hypertension and cognitive change after stroke was also observed in participants (n = 176) when cognitive function was measured with the mMMSE (adjusted $p = 0.036$). Although the direction of the association between pre-existing hypertension and cognitive change was similar when cognitive function was measured with DSST, sample size was small (n = 76) and the trend was not significant (adjusted $p = 0.26$). Exclusion of subjects with a history of stroke did not impact analyses (data not shown).

### *Pre-existing Hypertension and Cognitive Decline in Participants with Stroke Compared with Participants without Stroke*

Cognitive decline (defined by the median change in Trails B score between study visits for the entire co-

*Table 2. Odds of Cognitive Decline after Stroke Associated with Pre-existing Hypertension by Cognitive Test*[a]

| Cognitive Test | Subjects (n) | Crude OR (95% CI) | Adjusted OR (95% CI)[b] | Adjusted $p$[b] |
|---|---|---|---|---|
| Trails B | 119 | 4.27 (1.55–11.8) | 4.07 (1.37–12.1) | 0.01 |
| mMMSE | 176 | 2.30 (1.02–5.18) | 2.65 (1.09–6.46) | 0.03 |
| DSST | 76 | 2.40 (0.55–10.6) | 2.73 (0.43–17.3) | 0.39 |

[a]Cognitive decline was defined for each cognitive test based on the median change in score for the entire cohort. Hypertension is defined as systolic blood pressure >140mm Hg, diastolic blood pressure >90mm Hg, or taking antihypertensive medication.
[b]Adjusted for age at stroke, education, baseline cognitive test score, time between baseline and follow-up test, and time between stroke and follow-up test.

OR = odds ratio; mMMSE = modified Mini-Mental State Examination; DSST = Digital Symbol Substitution Test.

hort) was present in 64% (n = 76) of individuals who experienced an incident stroke between baseline and follow-up testing. After adjustment for demographic factors and the timing of the cognitive tests, pre-existing hypertension predicted cognitive decline in subjects with incident stroke (adjusted OR, 4.07; 95% CI, 1.37–12.1; $p$ = 0.01; Table 2). Baseline systolic and diastolic blood pressures considered individually also appeared to be related to the risk for cognitive decline among subjects with incident stroke. When analyzed by quartile, the relation between systolic blood pressure and cognitive decline after stroke appeared to be J-shaped (Fig).

In contrast to the large risk for cognitive decline associated with hypertension among subjects with incident stroke, hypertension was associated with only a slight increase in the risk for cognitive decline between visits (n = 10,359) in which subjects (n = 6,306) completed baseline and follow-up Trails B testing and did not have an intervening stroke (adjusted OR, 1.13; 95% CI, 1.04–1.22; $p$ = 0.002) (from generalized estimating equation model to adjust for lack of independence when the same subject completed multiple visits). Despite the wide CIs around the risk estimate in the group with stroke, this difference did not appear to be caused by chance ($p$ for interaction = 0.032), indicating that the risk for cognitive decline associated with hypertension was greater in stroke patients when compared with subjects without stroke. Similarly, when cognitive decline was measured with the mMMSE, the risk for decline associated with baseline hypertension appeared greater in those with stroke (adjusted OR = 2.65; 95% CI, 1.09–6.46; $p$ = 0.032) when compared with those without stroke (adjusted OR = 1.00; 95% CI, 0.92–1.09; $p$ = 0.97) ($p$ for interaction = 0.056). When baseline blood pressure was analyzed by quartile, the risk for cognitive decline associated with high systolic and diastolic blood pressures also appeared greater in those with incident stroke compared with those who did not have a stroke during the follow-up period (see Fig).

*Sensitivity Analyses*

Because 31% of participants with stroke died before the next study visit and 23% did not complete follow-up cognitive testing despite remaining in the study, we performed sensitivity analysis to assess whether this loss to follow-up was likely to bias our results. Biased relative risk estimates would be expected if loss to cognitive follow-up was associated with both pre-existing hypertension and a difference in the probability of cognitive decline. Baseline hypertension, however, was not associated with either death after stroke (OR = 0.83; 95% CI, 0.42–1.66; $p$ = 0.60) or missing follow-up cognitive testing (OR = 1.23; 95% CI, 0.56–2.73; $p$ = 0.61). Although participants in this study who died or who did not complete additional cognitive testing are likely to have had a greater incidence of cognitive decline than those who completed follow-up testing, this was not possible to test directly. However, even when we considered all individuals who either died or did not complete follow-up testing to have had cognitive decline on Trails B, the association between hypertension and cognitive decline was only marginally lower (OR = 2.60; 95% CI, 1.22–5.22; $p$ = 0.01). Analogously, risk estimates for the association between pre-existing diabetes or smoking with cognitive decline after stroke might be biased because loss to cognitive follow-up after stroke was more common in participants with these factors (see Table 1). However, when we considered all diabetic subjects and smokers who did not complete cognitive follow-up to have had cognitive decline, neither diabetes (OR = 0.97; 95% CI, 0.40–2.35; $p$ = 0.94) nor tobacco use (OR = 1.52; 95% CI, 0.43–5.32; $p$ = 0.51) were predictors of cognitive decline after stroke.

## Discussion

In a prospectively defined cohort for which cognitive function was measured both before and after incident stroke, we found that the presence of hypertension predicted greater declines in cognitive function when a stroke occurred. This association was consistent across different cognitive tests and when both baseline systolic

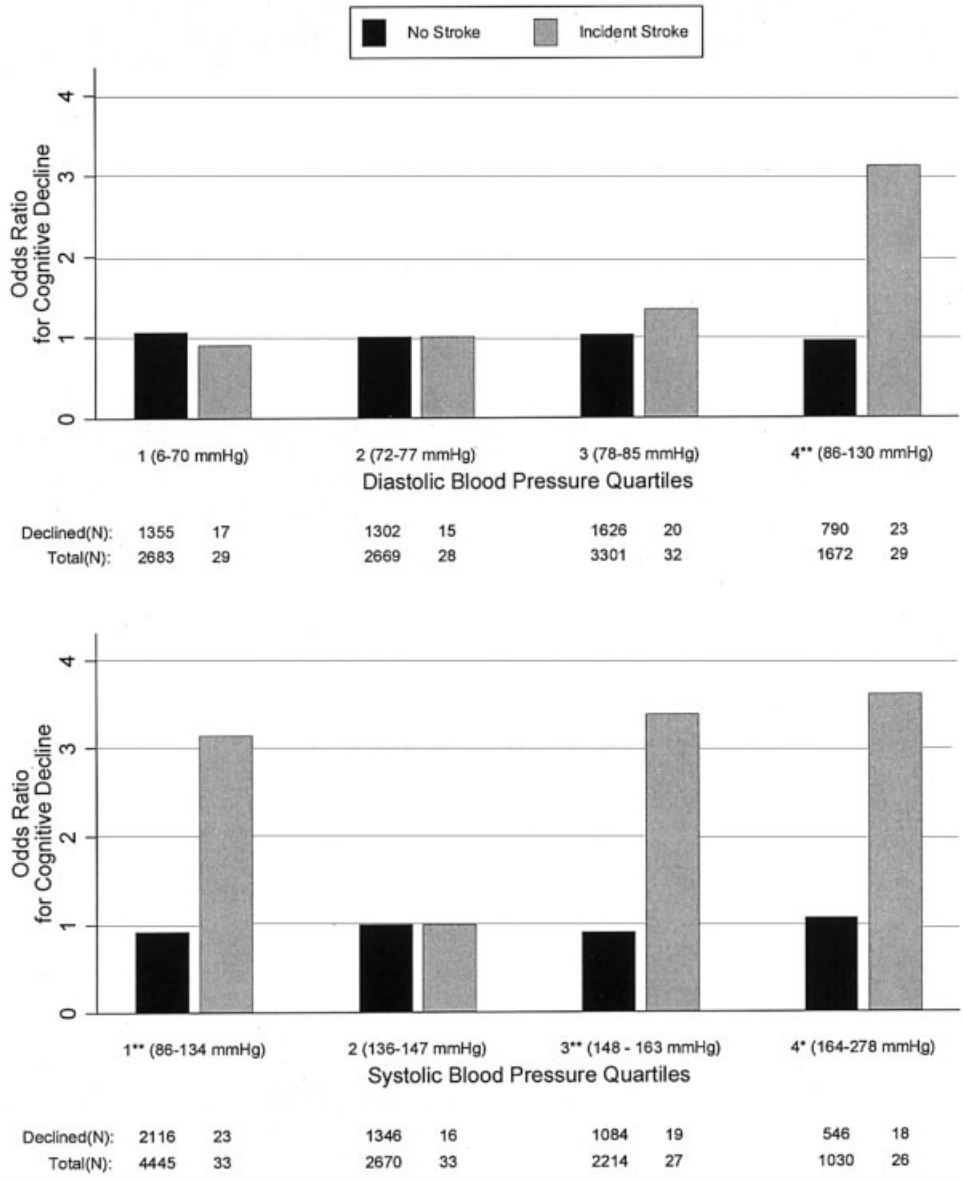


*Fig. Risk for cognitive decline associated with baseline systolic and diastolic blood pressure between visits with and without intervening stroke. All odds ratios are adjusted for age, education, baseline test score, and time between baseline and follow-up cognitive testing. Baseline blood pressure quartile was a stronger predictor of cognitive decline between visits when a stroke occurred compared with visits without an intervening stroke at* $^{*}p \leq 0.10$ *and* $^{**}p \leq 0.05$ *(p values from generalized estimating equation models to adjust for the nonindependence of repeated visits from the same subject.)*

and diastolic blood pressures were considered separately. Furthermore, this observation did not appear to be caused by a general association between hypertension and cognitive decline within the cohort.

Prior studies of stroke and cognitive function have identified subjects after a stroke has occurred.[1–4,20–22] These studies have documented that stroke is a risk factor for dementia and that characteristics such as age, education, diabetes, and recurrent medical illnesses may play an important role in predicting which individuals with stroke experience development of cognitive impairment. To our knowledge, our study is the first to report the change in cognitive function when measured both before and after a stroke has occurred. Therefore, our results provide a measure of the impact of the stroke event and its associated comorbidities on cognitive function as opposed to the association between stroke and an individual's future risk for cognitive decline. By measuring cognitive function longitudinally in individuals both with and without stroke, we are able to demonstrate that predictors of cognitive decline after stroke are not simply correlates of lower cognitive function before the stroke. Furthermore, this study design allowed us to demonstrate that the rela-

tion between hypertension and cognitive decline was stronger in those with incident stroke when compared with those without stroke.

Hypertension has been the strongest and most consistent predictor of subclinical brain injury as defined by magnetic resonance imaging markers such as silent infarct and leukoaraiosis.[5–7,23] Our results are consistent with the hypothesis that such injury could reduce the brain's ability to adapt or recover from stroke, thereby increasing susceptibility to cognitive decline. The lack of association between diabetes and current tobacco use with cognitive decline after stroke may have resulted from inadequate sample size and the known limitations of defining these exposures based on self-report.[24] Notably, however, neither diabetes nor current tobacco use were predictors of silent infarct in either the Cardiovascular Health Study or the Rotterdam Scan Study, the two largest studies to date of this pathology.[5,7,23] Therefore, the lack of association between these factors and cognitive decline after stroke could also reflect real differences in their relation to subclinical cerebral injury when compared with hypertension.

In contrast to the strong evidence of association between hypertension and silent infarct, the relation of hypertension to cognitive decline is more controversial. Generally, studies that have measured hypertension at midlife have found stronger associations with late-life cognitive decline than studies that have measured blood pressure in elderly adults.[25–29] Analyses of hypertension and cognitive decline in elderly adults are complicated by the tendency of blood pressure to decrease as cognitive decline progresses.[30] In addition, low blood pressures in some elderly adults may be associated with an increase in comorbid disease, a finding supported by the J-shaped relation between systolic blood pressure and cognitive decline observed in our and other studies.[17–19] The results of our study suggest the heterogeneous findings of past studies may also be partly related to issues of power because hypertension had only a weak association with cognitive decline in individuals without stroke. Additional cognitive insults, such as stroke, may increase the effect size and make the association between hypertension and cognitive decline easier to detect.

Other interpretations of the association between hypertension and cognitive decline after stroke are also plausible. Although the association could be explained by increased stroke severity among individuals with pre-existing hypertension, hypertension was not a predictor of mortality after stroke in this cohort. Furthermore, prior studies have not found a history of hypertension to be a predictor of greater acute stroke severity.[31] Similarly, because hypertension was not associated with stroke subtype in this analysis or in previous studies,[32] it is doubtful that differences in stroke location or size between hypertensive and normotensive subjects account for our results.

The strengths of our study include the ability to combine detailed cognitive function measurements with validated records of stroke within a large, community-based cohort study. The relations observed among hypertension, stroke, and cognitive decline were internally consistent when cognitive function was measured with both the Trails B and the mMMSE. Because only 66% of individuals included in the analysis of the mMMSE were also included in the analysis of the Trails B, this internal consistency is unlikely to result simply from correlation between the two test results in the same individual. There are also limitations. Although our results provide data about the long-term cognitive changes associated with stroke, we cannot distinguish the immediate impact of the stroke on cognitive function from that of the changes in functional and health status that accompany stroke. Because Trails B and DSST depend in part on vision and motor function, we cannot exclude the possibility that our findings may have been influenced by effects of stroke on sensorimotor systems apart from cognition. Our findings about the relation between hypertension and cognitive decline are likely to be generalized primarily to relatively healthy individuals with mild strokes. In individuals with severe strokes, pre-existing health factors may have little or no ability to modify the impact of stroke on cognitive function. Finally, it should be emphasized that our findings may not be generalized to men.

Several large-scale interventional trials have examined the impact of decreasing blood pressure on cognitive outcomes.[33–36] These studies generally have focused on the efficacy of treatment for preventing cognitive decline independently of stroke. Our findings suggest that reducing blood pressure may have a larger potential to reduce the burden of cognitive impairment among stroke survivors.

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